Controversies in cardiovascular medicine

Stroke and bleeding risk assessment in atrial fibrillation: when, how, and why?

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Received 2 October 2012; revised 3 November 2012; accepted 25 November 2012; online publish-ahead-of-print 20 December 2012

Decision making with regard to thromboprophylaxis should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient. As a consequence, a crucial part of atrial fibrillation (AF) management requires the appropriate use of thromboprophylaxis, and the assessment of stroke as well as bleeding risk can help inform management decisions by clinicians. The objective of this review article is to provide an overview of stroke and bleeding risk assessment in AF. There would be particular emphasis on when, how, and why to use these risk stratification schemes, with a specific focus on the CHADS2 [congestive heart failure, hypertension, age, diabetes, stroke (doubled)], CHA2DS2-VASc [congestive heart failure or left ventricular dysfunction, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female)], and HAS-BLED [hypertension (i.e. uncontrolled blood pressure), abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR (if on warfarin), elderly (e.g. age > 65, frail condition), drugs (e.g. aspirin, NSAIDs)/alcohol concomitantly] risk scores.

Keywords Stroke • Bleeding • Risk assessment • Atrial fibrillation

Introduction

Stroke prevention with appropriate thromboprophylaxis remains central to the comprehensive management of atrial fibrillation (AF).1,2 Stroke risk in AF is not homogeneous. Thus, decision making with regard to antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient. As a consequence, a crucial part of AF management requires the appropriate use of thromboprophylaxis, and assessment of stroke as well as bleeding risk to help inform management decisions.

The objective of this review article is to provide an overview of stroke and bleeding risk assessment in AF. There would be particular emphasis on when, how, and why to use these risk stratification schemes, with a specific focus on the CHADS2 [congestive heart failure, hypertension, age, diabetes, stroke (doubled)], CHA2DS2-VASc [congestive heart failure or left ventricular dysfunction, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female)], and HAS-BLED [hypertension (i.e. uncontrolled blood pressure), abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR (if on warfarin), elderly (e.g. age > 65, frail condition), drugs (e.g. aspirin, NSAIDs)/alcohol concomitantly] scores.

Stroke risk in atrial fibrillation

Over the last decade, various ways to assess stroke and bleeding risk have been proposed. Older stroke risk assessment has largely been based on various stroke risk factors identified from the non-warfarin arms of (now historical) clinical trial cohorts nearly two decades ago, and various epidemiological studies.3 These risk factors have been used to derive various stroke risk stratification schemes, or risk prediction tools—some of which have been used in clinical practice guidelines or consensus statements (Table 1).

However, the use of the historical trial cohorts for the assessment of stroke risk factors has been problematic as these trials only randomized a minority (< 10%) of patients screened for eligibility, many patients were withdrawn from warfarin therapy following inclusion into the trial, and many risk factors were not systematically recorded or consistently defined.3–5 Indeed, their generalizability to ‘real-world’ populations has even been questioned.5
More recent, large 'real-world' cohort studies have examined stroke risk factors in multiple independent AF populations. The various studies—including both old and new, as well as trial and non-trial cohorts—have recently been the subject of a detailed systematic review by Pisters et al., which complements other summaries of stroke risk factors in AF. From their systematic review on stroke risk factors, Pisters et al. found that a prior stroke or transient ischaemic attack [15 of 16 studies positive, risk ratio (RR) 2.86], hypertension (11 of 20 studies positive, RR 2.27), ageing (9 of 13 studies positive, RR 1.46 per decade increase), structural heart disease (9 of 13 studies positive, RR 2.0), and diabetes (9 of 14 studies positive, RR 1.62) were found to be good independent predictors of stroke. Additional supportive evidence was found for female gender (8 of 22 studies positive, RR 1.67), vascular disease (6 of 17 studies positive, RR 2.61), and heart failure (7 of 18 studies positive, RR 1.85).

Despite stroke risk in AF being a continuum, the older stroke risk stratification schemes have been used to 'artificially' categorize patients into 'low-', 'moderate-', and 'high'-risk strata, so that the AF patients at highest risk can be identified for vitamin K antagonist (VKA, e.g. warfarin) therapy, which was—until recently—the only type of oral anticoagulant available for thromboprophylaxis. Vitamin K antagonist was an 'inconvenient' drug with the need for regular monitoring to keep within a narrow therapeutic range [international normalized ratio (INR) 2.0–3.0] and was associated with a significant risk of bleeding (especially intracranial haemorrhage) particularly in the early period following its initiation. Thus, if anyone was to be targeted for VKA therapy, those at 'high risk' would be the patient group targeted.

The categorization into low-, moderate-, and high-risk strata is an oversimplification (and artificial)—and clinically, this was problematic, as the predictive value of such a focus on identifying 'high-risk' patients was modest at best, when evaluated using the c-statistic (most had a c-statistic of ~0.6, where 0.5 is by chance and 1.0 is the perfect predictive value). Nonetheless, the c-statistic may also not be the best way to assess the value of a score, with reclassification now being the preferred option; thus, comparisons of risk scores should also include the net reclassification improvement and integrated discrimination improvement. In addition, c-statistics in one published study should not be compared with another given the heterogeneity between study populations and stroke risk profiles. Furthermore, prescribing of oral anticoagulants has little relationship to the low-, moderate-, and high-risk strata, as the proportions being prescribed VKAs are broadly similar in all three strata.

The 'moderate-risk' category was also problematic as older guidelines recommended 'warfarin or aspirin' in these patients, and schemes that categorized a large proportion of patients within this category were less useful, as clinicians were left with the uncertainty over whether 'aspirin or warfarin' should be prescribed. In the study by Fang et al., some stroke risk stratification scores classified up to 61% of patients into this 'moderate-risk' category.

### Table 1  Risk factors included in various stroke risk stratification schemes and published guidelines

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<th>Risk stratification schemes</th>
<th>Risk factor</th>
<th>Age</th>
<th>Female</th>
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<th>Hypertension</th>
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Guidelines and consensus statements

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ACCP, American College of Chest Physicians; AF, Atrial Fibrillation Investigators; CHADS\(_2\), C—congestive heart failure, H—hypertension, A—age ≥75, D—diabetes mellitus, S—previous stroke/TIA; CHADS\(_2\)-VASc, C—congestive heart failure or left ventricular dysfunction, H—hypertension, A\(_2\)—age ≥75, D—diabetes mellitus, S—previous stroke/TIA/systemic embolism, V—vascular disease, A—age 65–74, Sc—sex category female; ESC, European Society of Cardiology; RCPE, Royal College of Physicians of Edinburgh; SPAF, Stroke Prevention in Atrial Fibrillation.

\(^a\)Age and female gender combined are a single risk factor.
The changing landscape of antithrombotic therapy

The diminishing role of aspirin

In the historical trials, VKA therapy resulted in a significant 64% (95% CI 49–74) reduction in stroke and a 26% (95% CI 3–43) reduction in all-cause mortality, compared with placebo/control. In contrast, antiplatelet therapy reduced strokes by 22% (95% CI 6–35) compared with control, but when the analysis was confined to aspirin-only trials, aspirin produced a non-significant 19% (95% CI –1 to 35) reduction in the incidence of stroke, with no significant effect on mortality (relative risk reduction 14%, 95% CI –7 to 31). Even this 19% stroke reduction with aspirin was driven by one single positive trial, the SPAF-1 study, which reported a 42% stroke risk reduction with aspirin 325 mg daily vs. placebo, with important internal heterogeneity for the aspirin effect between the anticoagulation-eligible and anticoagulation-ineligible arms of the trial (94 vs. 8% stroke risk reduction). Also, aspirin was ineffective in patients older than 75 years and did not prevent severe strokes.

More recently, the role of aspirin for stroke prevention in AF has been much more debated. With increasing age (where the prevalence of AF also increased), the beneficial effect of warfarin on reducing ischaemic stroke increased, while it decreased for aspirin as patients got older. Indeed, aspirin is minimally effective for preventing strokes, and may not be any safer when compared with warfarin, especially in the elderly. Among the elderly, warfarin is superior to aspirin for preventing thromboembolism, and the rates of major bleeding (including intracranial haemorrhage) in recent randomized trials and large cohort studies were not significantly different between warfarin and aspirin.

Novel oral anticoagulants

Another driving force for the paradigm shift has been the availability of novel oral anticoagulants (NOACs), which have had large Phase 3 clinical trials demonstrating efficacy, safety, and convenience compared with VKA therapy. The NOACs are in two main drug classes: the oral direct thrombin inhibitors (e.g. dabigatran) and oral Factor Xa inhibitors (e.g. rivaroxaban, apixaban). All these agents have shown at least non-inferiority to warfarin therapy, and in some cases superior efficacy for the primary endpoint of stroke and systemic embolism [dabigatran 150 mg twice a day (b.i.d.), apixaban] or ischaemic stroke (dabigatran 150 mg b.i.d.). Importantly, all the NOACs show significantly less haemorrhagic stroke and intracranial haemorrhage, compared with warfarin.

In one trial with an NOAC, apixaban, among AF patients who had refused, failed, or deemed ineligible for warfarin, was superior to aspirin 81–324 mg daily, with similar rates of major bleeding and intracranial haemorrhage. Nonetheless, an appreciation of these trial treatment effects requires thoughtful assessment of how their results should be placed in the context of patients studied in the trials and how those patients, and the results of the trials, extrapolate to general population data, which will require information from post-marketing cohort studies.

Current guidelines recommend that the NOACs are broadly preferable to VKA therapy in the vast majority of patients with non-valvular AF. In the absence of head-to-head trials, indirect comparison analyses do not suggest profound differences in efficacy endpoints between the NOACs, but major bleeding appears lower with dabigatran110 mg b.i.d. and apixaban. Ancillary analyses from the trials with dabigatran and apixaban suggest that the NOACs maintain their efficacy and safety compared with warfarin, even when assessed in relation to their stroke and bleeding risk strata, based on CHADS2, CHA2DS2-VASc, and HAS-BLED scores.

In a Markov model balancing ischaemic stroke reduction against intracranial haemorrhage, as well as a quality-of-life utility, the threshold for warfarin treatment was found to be a stroke rate of 1.7%/year, but for a NOAC, this ‘tipping point’ threshold for treatment would be reduced to 0.9%/year. Indeed, the trial data with the NOACs all consistently show a 30–70% lower risk of intracranial haemorrhage compared with VKA therapy, and apixaban did not increase major or intracranial bleeding compared with aspirin. As mentioned above, the major or intracranial bleeding rates with warfarin and aspirin are not markedly different, in contemporary ‘real-world’ cohorts, at least in countries with good anticoagulation control. Thus, the threshold for the use of the NOACs should perhaps be as low as a predicted stroke risk of 1% per year. Other modelling analyses against ‘real-world’ stroke and bleeding rates clearly show the NOACs to have a positive net clinical benefit even among those with a CHA2DS2-VASc score ≥1, when balancing ischaemic stroke against intracranial bleeding.

Optimizing vitamin K antagonist use

The NOACs are not the only reason for the shift towards effective stroke prevention with oral anticoagulation. Indeed, there is now greater awareness on how to optimize VKA use, so that it would be less ‘inconvenient’ and dangerous. For example, efforts to improve anticoagulation control have led to greater average time in therapeutic range (TTR), which has been associated with lower risks of stroke and bleeding outcomes. Indeed, a target TTR of ≥70% is recommended in a recent European position document. Anticoagulation management has also been improved by the use of self-monitoring and point-of-care testing, which offers better outcomes compared with standard care. Pharmacogenetics of warfarin are also better understood, and could offer some improvements in warfarin dosing. Nonetheless, there still remains wide global variation in warfarin use as well as the quality of INR control, as reflected by the average TTR. Of note, ancillary analyses from randomized trials of the NOACs suggest that the relative efficacy is maintained irrespective of average centre-based (and not individual) TTRs. Thus, the efficacy difference between (say) warfarin and dabigatran in the top quartile of centre-based TTR is less apparent, compared with those in the lower quartile of centre-based TTR.

With new information on risk factors, the recognition that aspirin has a limited role, improvements in anticoagulation control with the VKAs (to achieve high TTRs), and the availability of NOACs that are alternatives to warfarin, the paradigm shift has been directed towards being more inclusive (rather than exclusive) of stroke risk factors, to get better at identifying the ‘truly low-risk patients’ with AF. Once such patients are identified, they do not need any antithrombotic therapy given their low absolute risk of stroke—hence, all other AF patients with ≥1 stroke risk factors can be offered effective stroke prevention, which is essentially oral anticoagulation.
The CHADS\textsubscript{2} score

A simple and commonly used stroke risk assessment tool is the CHADS\textsubscript{2} score, which was the amalgamation of the AF Investigators and SPAF trial stroke risk stratification schemes, based on data from the non-VKA arms of the historical trial cohorts.\textsuperscript{42} This score includes five common stroke risk factors, congestive heart failure, hypertension, age $\geq 75$, diabetes, and prior stroke, the latter getting 2 points. Since its original validation in 2001 in the NRAF cohort of hospitalized AF patients, the CHADS\textsubscript{2} score has been widely validated in numerous cohorts. All have consistently shown that the predictive value of the CHADS\textsubscript{2} score for predicting stroke/thromboembolism was only modest (c-statistic $\approx 0.6$).\textsuperscript{4,42,43}

As per its original validation paper, a CHADS\textsubscript{2} score $= 0$ was deemed ‘low risk’, a score of $1–2$ was ‘moderate/intermediate risk’, and a score of $\geq 3$ was ‘high risk’. This was initially problematic, as a patient with AF and ‘prior stroke’ only as a single risk factor would be classed as ‘moderate risk’, despite such patients (a secondary prevention cohort) being at highest risk for subsequent stroke and thromboembolism. Such a categorization would also classify nearly 60–65\% of AF patients as ‘moderate/intermediate risk’, whereas older guidelines would recommend ‘warfarin or aspirin’ for such patients.\textsuperscript{9} Also, a 74-year-old female patient with peripheral artery disease would be categorized as a CHADS\textsubscript{2} score $= 0$, implying that such patients are at ‘low risk’ when they are clearly not so (and most clinicians would offer anticoagulation to such a hypothetical patient).

The pros and cons of the CHADS\textsubscript{2} score have been carefully debated.\textsuperscript{44,45} One recent systematic review and meta-analysis also concluded that the pooled c-statistic and calibration analysis suggested minimal clinical utility of the CHADS\textsubscript{2} in predicting ischaemic stroke across all risk strata, and even suggested that further validation of CHADS\textsubscript{2} should perhaps be undertaken.\textsuperscript{46}

Other data from ancillary analyses of more recent trial cohorts have shown that patients with a CHADS\textsubscript{2} score $= 1$ derived benefit from VKA therapy.\textsuperscript{47–49} Thus, more recent contemporary guideline updates have reclassified the CHADS\textsubscript{2} score, as score $0 = $ low risk, $1 = $ moderate risk and $\geq 2 = $ high risk.\textsuperscript{50} More recent guidelines have even changed the recommendations for starting oral anticoagulation for subjects with a CHADS\textsubscript{2} score of $\geq 1$.\textsuperscript{4,42,47}

There was also some ambiguity over some components of the CHADS\textsubscript{2} score. For example, did the ‘C’ represent decompensated heart failure (as originally validated in 2001),\textsuperscript{42} but not based on the AF Investigators or SPAF schemes, or as has increasingly been used by guidelines to indicate ‘any heart failure’? This is relevant as the large, comprehensive systematic review of stroke risk factors by the Stroke in AF Working Group concluded that heart failure was not a significant nor consistent risk factor for stroke/thromboembolism.\textsuperscript{7} This was also seen in the large Swedish AF cohort study, where heart failure was not an independent predictor for stroke on multivariate analysis.\textsuperscript{22} However, the presence of moderate/severe left ventricular systolic impairment on echocardiography was clearly an independent stroke risk factor.\textsuperscript{51} Of the many patients labelled as ‘heart failure’, only 50\% have systolic impairment.\textsuperscript{52} Indeed, the stroke risk with AF and heart failure with preserved ejection fraction (HFpEF) was unclear, with only limited data available. In a large contemporary cohort, recent acute decompensated heart failure requiring hospitalization was a stroke risk factor—whether related to heart failure with reduced ejection fraction, or HFpEF.\textsuperscript{53} In a small study by Jang et al.,\textsuperscript{38} the 3-year risks of for ischaemic stroke (HR 3.29; 95\% CI 1.58 to 6.86; $P < 0.001$), death (HR 5.52; 95\% CI 2.24 to 13.63; $P < 0.001$), and composite of ischaemic stroke and death (HR 4.08; 95\% CI 2.30 to 7.26; $P < 0.001$) were significantly higher in patients with AF and HFpEF.

Also, did the ‘H’ in the CHADS\textsubscript{2} score represent any history of hypertension or uncontrolled blood pressure? In the historical trials, from which the validation of the CHADS\textsubscript{2} score was derived, ‘hypertension’ was defined as ‘history of hypertension’ or systolic blood pressure $>160 \text{mmHg}$, i.e. uncontrolled hypertension. More contemporary cohorts suggest that well-controlled hypertension in AF patients was associated with a low stroke risk.\textsuperscript{55–57} Nonetheless, a long history of prior hypertension (even if well controlled more recently) could be associated with vascular changes (including small vessel disease on cerebral imaging) that may contribute to increased stroke risk.

Does a CHADS\textsubscript{2} score $= 0$ represent low risk? Recent studies have shown how such patients are not ‘low risk’. A recent study from a large nationwide cohort shows that among $>70,000$ AF patients with a CHADS\textsubscript{2} score $= 0$, the stroke and thromboembolism rate could vary between 0.8\%/year and 3.2\%/year\textsuperscript{58} (Figure 1). Of the patients with a CHADS\textsubscript{2} score $= 1$, the stroke and thromboembolism rate could even be as high as 8.1\%/year.\textsuperscript{58} In a similar analysis of a trial cohort, some patients with AF and a CHADS\textsubscript{2} score of 1 could be identified, who were unlikely to benefit from oral anticoagulant therapy.\textsuperscript{59}

Even in its original validation study, a CHADS\textsubscript{2} score $= 0$ had a stroke rate of 1.9\%/year,\textsuperscript{42} which is on the threshold for primary prevention intervention (for example, with statins), and as stated earlier, the threshold for starting oral anticoagulation may be a predicted stroke rate that is as low as 1\%.

Finally, the CHADS\textsubscript{2} score does not include many common risk factors for stroke in AF. For example, the risk of stroke in AF rises with increasing age, from age 65 upwards\textsuperscript{19,60–62} (and not age 75, as in the CHADS\textsubscript{2} score)—and stroke risk is a continuum. The stroke risk of patients aged $\geq 75$ is nearly two-fold greater than those aged 65–74 years.\textsuperscript{22} Indeed, a powerful continuous variable like age loses some predictive ability if dichotomized or even in three groups, and the discrimination ability could improve if it was used as a continuous (or more finely stratified, like in 5-year increments) variable.\textsuperscript{5,63} However, this approach would lose simplicity and practicality for everyday clinical use.

Also, the CHADS\textsubscript{2} score does not consider vascular disease as a risk factor, as this was poorly defined (or not systematically looked for, nor recorded) in the historical trial cohort datasets. However, the presence of vascular disease, whether peripheral artery disease, prior myocardial infarction, or complex aortic plaque on transoesophageal echocardiography, is an independent risk factor for stroke.\textsuperscript{22,62,64}

Female sex is also an independent risk factor for stroke in AF, increasing the risk by $\approx 18\%$, a similar risk as for hypertension or diabetes.\textsuperscript{62,65} However, this risk is age dependent, and in patients aged $<65$, female gender is not an independent risk factor for
stroke. Also, absolute event rates in female patients aged <65 with lone AF (despite having a CHA2DS2-VASc score = 1 on the basis of gender alone) are so low that no antithrombotic therapy is reasonable.1

The CHA2DS2-VASc score

The original Birmingham stroke risk schema was adapted from the AF Investigators stroke risk stratification scheme and modified into an algorithm-based risk stratification that included age 65–74 and vascular disease as additional stroke risk factors to consider as part of any comprehensive stroke risk assessment. This scheme was adapted and subsequently validated for the United Kingdom National Institute for Health and Clinical Excellence (NICE) guideline on AF (2006), where the stroke risk stratification algorithm classified patients into low-, moderate-, and high-risk strata.69,70 Also, the 2006 American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines for AF listed age 65–74, female gender, coronary artery disease, and thyrotoxicosis as ‘weaker or less validated’ stroke risk factors, although the main stroke risk assessment was based on the CHADS2 score.15

The CHA2DS2-VASc score was first proposed in 2009 (published online 17 September 2009)71 and first validated in an European cohort from the EuroHeart survey, but subsequently validated in multiple independent epidemiological and trial cohorts.3,60,72,73 The CHA2DS2-VASc score was designed as a simple stroke risk assessment that was more inclusive of common stroke risk factors in AF, and to give extra weight to ‘age ≥75’ with 2 points, and to add in age 65–74, female gender, and vascular disease as additional stroke risk factors (1 point each)74 (Table 2).

This score consistently performs best in the identification of ‘truly low-risk’ patients with AF who do not need any antithrombotic therapy, given their low absolute stroke risk.75 In the Belgrade AF Project, the CHA2DS2-VASc score was the only score that significantly predicted the absence of stroke, while the CHADS2 and van Walraven scores did not significantly do so.76 The CHA2DS2-VASc score performs at least as good as—and possibly better than—the CHADS2 score in identifying ‘high-risk’ patients who subsequently develop stroke and thromboembolism.22,60,73,75 Also, the CHA2DS2-VASc score classifies only a small proportion (<15%) as ‘moderate risk’, based on a CHA2DS2-VASc score = 1.75

In patients undergoing ablation, the CHA2DS2-VASc score could be used to further stratify the patients with CHADS2 scores of 0–1 into those at low risk (0.6%/year, i.e. CHA2DS2-VASc score = 0) for subsequent thromboembolism.77 Similar data were observed in a clinical trial cohort, where the CHA2DS2-VASc score could identify a subset of patients with CHADS2 scores of 0–1 at low risk where anticoagulation was not warranted.59

What do the guidelines say?

The 2010 European Society of Cardiology guidelines de- emphasized the ‘artificial’ low-, moderate-, and high-risk

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**Figure 1** The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with a CHADS2 score 0–1 (based on Olesen et al.)58
categorization and recommended a risk factor-based approach to stroke risk assessment, with the CHA$_2$DS$_2$-VASc score used to complement the CHADS$_2$ score. The guideline treatment algorithm used the CHA$_2$DS$_2$-VASc risk factors to further refine stroke risk stratification in those with a CHADS$_2$ score 0–1.

The 2012 ACCP guidelines recommend stroke risk assessment initially using the CHADS$_2$ score, where oral anticoagulation is recommended for CHADS$_2$ score of $\geq 1$, and then considering age 65–74, female gender, and vascular disease as additional ‘non-CHADS$_2$ risk factors’, as the presence of multiple ‘non-CHADS$_2$ risk factors’ would again merit anticoagulation.

The 2012 focussed update of the Canadian Cardiovascular Society guidelines recommends the use of oral anticoagulation for a CHADS$_2$ score $\geq 1$, and among those with a CHADS$_2$ score = 0, the consideration of age 65–74, female gender, and vascular disease, where the absence of all these risk factors merited ‘no antithrombotic therapy’. The ACC/AHA/HRS guidelines and the UK NICE guidelines are still being updated from their full 2006 text that discusses stroke risk stratification, although a focused update of the American guidelines incorporated sections on new drugs, such as dabigatran and dronaderone, into a 2011 limited update.

The 2012 focussed update of the ESC guideline only recommends the CHA$_2$DS$_2$-VASc score for stroke risk assessment. Very importantly, this guideline strongly recommended a clinical practice shift towards more focus on identification of ‘truly low-risk’ patients with AF, instead of trying to focus on identifying ‘high-risk’ patients. These ‘truly low-risk’ patients were defined as ‘age $< 65$ years and lone AF (irrespective of gender) or CHA$_2$DS$_2$-VASc score = 0’, and these do not need any antithrombotic therapy. Oral anticoagulation (whether as well-controlled VKA or a NOAC) is recommended for patients with a CHA$_2$DS$_2$-VASc score $\geq 2$ (Class I recommendation), while oral anticoagulation should be considered for patients with a CHA$_2$DS$_2$-VASc score = 1 (Class IIa recommendation) (Figure 2).

In the setting of ablation, stroke risk assessment is recommended when deciding on whether oral anticoagulation can be

| Table 2 Stroke and bleeding risk stratification with the CHA$_2$DS$_2$-VASc and HAS-BLED schemas |
|-----------------------------------------------|-----------------|-----------------|
| **CHA$_2$DS$_2$-VASc** | **Score** | **HAS-BLED** | **Score** |
| Congestive heart failure/LV dysfunction | 1 | Hypertension, i.e. uncontrolled BP | 1 |
| Hypertension | 1 | Abnormal renal/liver function | 1 or 2 |
| Age $\geq 75$ years | 2 | Stroke | 1 |
| Diabetes mellitus | 1 | Bleeding tendency or predisposition | 1 |
| Stroke/TIA/TE | 2 | Labile INRs (if on warfarin) | 1 |
| Vascular disease (prior MI, PAD, or aortic plaque) | 1 | Age (e.g. $> 65$, frail condition) | 1 |
| Aged 65–74 years | 1 | Drugs (e.g. concomitant aspirin or NSAIDs) or alcohol excess/abuse | 1 |
| Sex category (i.e. female gender) | 1 | | |
| Maximum score | 9 | | 9 |

CHA$_2$DS$_2$-VASc: C—congestive heart failure or left ventricular dysfunction, H—hypertension, A$_2$—age $\geq 75$, D—diabetes mellitus, S$_2$—previous stroke/TIA/systemic embolism, V—vascular disease, A—age $65–74$, Sc—sex category female; HAS-BLED: Hypertension (i.e. uncontrolled blood pressure), Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INRs (if on warfarin), Elderly (e.g. age $> 65$, frail condition), Drugs (e.g. aspirin, NSAIDs)/alcohol concomitantly; LV, left ventricular; BP, blood pressure; INR, international normalized ratio; TIA/TE, MI, myocardial infarction; PAD, peripheral artery disease; NSAIDs, non-steroidal anti-inflammatory drugs.

Figure 2 Flow diagram from the 2012 European Society of Cardiology focused update guideline on atrial fibrillation. Initial focus on identification of ‘truly low risk’, i.e. age $< 65$ and lone atrial fibrillation (irrespective of gender) or CHA$_2$DS$_2$-VASc score = 0. Female patients who are aged $< 65$ and have lone atrial fibrillation (but still have a CHA$_2$DS$_2$-VASc = 1 by virtue of their gender) are at low risk and no antithrombotic therapy should be considered.
discontinued post-ablation, and long-term oral anticoagulation is recommended in patients with CHA2DS2-VASc score ≥2.

How do we improve on risk scores based on clinical risk factors?

The CHADS2 and CHA2DS2-VASc score offer simplicity and practicality for everyday clinical use. These scores also assume that each clinical risk factor carries equal weight (i.e. score = 1 point) apart from stroke or age ≥75 (both 2 points), although this is clearly an over-simplification and the various studies suggest otherwise. For example, when compared with age <65, age 65–74 increases risk 2.9-fold and age ≥75, 5.3-fold; also, female gender, hypertension, and diabetes only increases stroke risk by ~18%.

Can stroke risk assessment be further refined? Clearly, the measurement of a ‘biomarker’ whether a blood test, urinalysis (e.g. for proteinuria), or imaging modality offers additional precision and can improve on stroke risk assessment. These biomarkers require derivation and validation in large ‘real world’ non-anticoagulated cohorts, and not highly selected clinical trial populations that are based on specific trial inclusion/exclusion criteria (e.g. most trials exclude severe renal failure, with a creatinine clearance <30mls/min).

Even assessment of AF burden can improve on stroke risk stratification using clinical criteria. In the study by Boriani et al. there was a marked improvement in c-statistic from 0.65 to 0.71 ($P = 0.007$) with the CHADS2 score by the addition of AF burden, while for the CHA2DS2-VASc score, there was only a very modest change in c-statistic.

Echocardiography is undertaken in most patients with AF, and as previously stated, the presence of moderate–severe left ventricular systolic dysfunction on two-dimensional echocardiography is an independent predictor of stroke. On transoesophageal echocardiography, the presence of spontaneous echocontrast, low left atrial appendage velocities, left atrial appendage thrombus, and complex aortic plaque on the descending aorta are independent predictors of thromboembolism. Clearly, detailed echocardiography can offer additional precision on assessing the potential for stroke and thromboembolism. Again, to mandate echocardiographic assessments in everyone with AF would confer additional complexity for everyday clinical use.

Blood biomarkers have attracted much interest to refine clinical risk stratification. Indeed, AF is associated with a prothrombotic or hypercoagulable state, with abnormalities of coagulation, platelets, and endothelial indices that could function as potential biomarkers. Plasma von Willebrard factor (vWF, an index of endothelial damage/dysfunction) and fibrin D-dimer (a fibrin degradation product) have also been shown to have prognostic implications in AF patients. In contrast, inflammatory parameters such as C-reactive protein are predictive of death but not stroke in AF, consistent with the predictive performance of C-reactive protein in patients with vascular disease. Lip et al. first reported that the use of plasma vWF improved the predictive value of the CHADS2 score for stroke and death in a cohort of AF patients participating in the SPAF-III trial. More recently, troponin and naturess peptide levels had independent prognostic value in the anticoagulated RE-LY trial population.

Renal (dys)function, whether assessed by creatinine clearance, eGFR, or simply proteinuria, is also a consideration. Renal failure patients have largely been excluded from clinical trials, and their risk assessment balancing stroke and bleeding risk is complex. The presence of renal impairment increases not only stroke risk but also the risk of bleeding, death, and coronary events. In the analysis by Olesen et al. patients with non-end-stage chronic kidney disease had an increased risk of stroke or systemic thromboembolism (HR 1.49; 95% CI 1.38 to 1.59; $P < 0.001$), as did those requiring renal-replacement therapy (HR 1.83; 95% CI. 1.57 to 2.14; $P < 0.001$); this risk was significantly reduced by warfarin but not with aspirin.

Also, renal dysfunction is closely associated with heart failure, hypertension, age, diabetes mellitus and vascular disease, which are the components of the CHADS2 and CHA2DS2-VASc scores. Until further study and validation in prospective studies, it was first proposed in 2010 that the lower case ‘c’ in CHA2DS2-VASc could informally be used to give an extra 1 point for the presence of renal (dys)function, whether assessed by creatinine clearance, eGFR, or proteinuria. In a small study of 547 selected patients undergoing ablation, renal dysfunction, as defined using estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m², could further risk stratify them into two groups with different event rates (4.3 vs. 0.3%, $P = 0.046$). If one more point representing renal dysfunction was added to the CHA2DS2-VASc score, the c-statistic was marginally increased from 0.84 to 0.88 ($P = 0.043$).

Detailed cerebral imaging may also help in assessing stroke and bleeding risk. The presence of small-vessel disease is a risk factor for stroke, although data in AF cohorts per se are lacking. The presence of small-vessel disease should be suspected from gait apraxia, impaired cognitive function, and incontinence, in the AF patients with risk factors such as hypertension. Also, cerebral microbleeds are potentially a risk factor for stroke and cerebral bleeding, although data are limited in AF cohorts. In contrast to studies reflecting a high incidence of microbleeds in stroke patients of various subtypes, one small study suggested that microbleeds may occur less frequently in patients with cardioembolic acute ischaemic stroke associated with non-valvular AF.

In summary, the value of clinical risk scores would be enhanced by biomarkers that can include blood markers (e.g. vWF), urine (e.g. proteinuria, eGFR or creatinine clearance), cardiac imaging (echocardiography, whether transthoracic or transoesophageal) and/or cerebral imaging (e.g. CT or MRI imaging) which can offer incremental predictive value for the identification of ‘high risk’ subjects. However, this would be at the cost of reduced simplicity and practicality, limiting its (immediate) ‘quick’ use in everyday clinical practice.

Bleeding risk factors

Bleeding risk assessment is more complex and many risk factors for bleeding are also risk factors for stroke. Risk factors for bleeding, as well as methods of assessment and bleeding risk scores have been comprehensively reviewed in a joint consensus document of the European Heart Rhythm Association and the ESC Working Group on Thrombosis.

Many risk factors for bleeding have been identified, but even as recent as 2008, only four bleeding risk scores have been applied to
AF populations while only one score (HEMORR\textsubscript{H}AGES) was derived and validated in an AF population.\textsuperscript{98}

In 2010, the HAS-BLED score (Table 2) was first proposed, having been derived and validated in the EuroHeart survey population.\textsuperscript{99} The HAS-BLED score has since been validated in multiple independent populations, where it performed as good as (and sometimes better) than the more complex HEMORR\textsubscript{H}AGES score.\textsuperscript{22,99,100} There is a close correlation between increasing HAS-BLED score and major bleeding or intracranial haemorrhage.\textsuperscript{22} In one analysis of anticoagulated AF patients, the HAS-BLED score was a good predictor of major bleeding (as good as a multivariable analysis) and only a modest predictor of cardiovascular events and death (less good compared with a multivariable analysis).\textsuperscript{101}

In 2011, another bleeding risk score in anticoagulated AF patients was proposed, called the ATRIA score, following its derivation and validation in a selected anticoagulated AF patient cohort.\textsuperscript{102} The limitations of this score have been highlighted and discussed.\textsuperscript{103} Since then, the HAS-BLED score has been shown to outperform the older HEMORR\textsubscript{H}AGES and less practical ATRIA scores in predicting clinically relevant bleeding in multiple ‘real-world’ and trial cohorts.\textsuperscript{104–106} Also, the HAS-BLED score was the only tested score to have a significant (and good, c-statistic 0.75) predictive value for intracranial haemorrhage.\textsuperscript{104} A high HAS-BLED score (≥3) is predictive of major bleeding during bridging therapy, in both AF and non-AF patients.\textsuperscript{107}

A high HAS-BLED score (≥3) is indicative of the need for regular review and follow-up, but should not be used as a reason for stopping oral anticoagulation per se.\textsuperscript{1,108} The HAS-BLED score also makes clinicians think about the potentially correctable risk factors for bleeding, for example, uncontrolled blood pressure (the H in HAS-BLED), labile INRs if on warfarin (the L in HAS-BLED), and concomitant use of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) (the D in HAS-BLED).

Of note, the ‘labile INR’ criterion only applies in a patient who is already taking warfarin—if the HAS-BLED score is being used to assess a non-anticoagulated patient’s potential bleeding risk in an informed manner, then the ‘labile INR’ criterion scores zero. However, after the patient has started on warfarin but comes back subsequently for a review, then the ‘labile INR’ criterion should be assessed if the concerned physician re-assesses bleeding risk (especially since INR values should be available), especially since risk assessment (whether for stroke or bleeding) is a dynamic process, and should be repeated at regular intervals.

The HAS-BLED score has been used in recommendations pertaining to the management of AF patients presenting with an acute coronary syndrome and/or undergoing percutaneous coronary stenting,\textsuperscript{109–111} as well as in the recent ESC guidelines on the management of acute and chronic heart failure\textsuperscript{112} and when formulating guideline recommendations for the NOACs in the 2012 focused update of the ESC guidelines.\textsuperscript{5} However, with the NOACs, the beneficial impact seems to be evident irrespective of HAS-BLED strata,\textsuperscript{31} and indeed, the net clinical benefit for OAC is greater at high HAS-BLED scores.\textsuperscript{113}

The AF guidelines recommend that the HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates ‘high risk’ and some caution and regular review are needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (Class IIa, LoE = A).\textsuperscript{1} Correctable risk factors for bleeding (e.g. uncontrolled blood pressure (e.g. systolic blood pressure > 160 mmHg), labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol excess/abuse, etc.) should be addressed (LoE = B). The HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not on its own be used to exclude patients from OAC therapy (LoE = B).

Balancing stroke and bleeding risk

How does one balance stroke and bleeding risk assessment? On the most simplistic level, one can balance the risk of ischaemic stroke (which is what we are trying to prevent with oral anticoagulation) against the risk of the most serious bleeding complication, intracranial haemorrhage.\textsuperscript{114}

Such a net clinical benefit analysis has been undertaken by Olesen et al.,\textsuperscript{23} who showed that the only category of patients where the net clinical benefit was negative with warfarin therapy was a CHA\textsubscript{2}DS\textsubscript{2}-VASc score = 0, reflecting the ‘truly low-risk’ status of such patients. The patients with a high HAS-BLED score (≥3) derived a higher net clinical benefit given that their absolute gain in ischaemic stroke reduction far outweighed the small increase in intracranial bleeding. There was no category of patient’s stroke or bleeding risk where aspirin had a positive net clinical benefit, leading to the author’s conclusion that aspirin should not be used for stroke prevention in AF.

Broadly similar findings were observed by Friberg et al.,\textsuperscript{113} who concluded that warfarin should perhaps be more widely used in AF patients given that the net clinical benefit was in favour of its use for most patients, again with the exception of a CHA\textsubscript{2}DS\textsubscript{2}-VASc score = 0.

Other methods to assess net clinical benefit would be the proposal by Connolly et al.\textsuperscript{115} to consider ischaemic events (ischaemic stroke or myocardial infarction) and haemorrhagic events (haemorrhagic stroke or subdural or extracranial bleeding), weighted by the hazard ratio for death (or death or disability) after an event relative to death (or death or disability) after ischaemic stroke. In an analysis of the ACTIVE trial data set, Connolly et al.,\textsuperscript{115} found that adding clopidogrel to aspirin therapy prevented 0.57 ischaemic stroke equivalents (95% CI, −0.12 to 1.24) per 100 patient-years of treatment when weighted by hazard for death after ischaemia or haemorrhage and 0.67 ischaemic stroke equivalents (CI, −0.03 to 1.18) when weighted by death or disability after ischaemia or haemorrhage. They concluded that adding clopidogrel to aspirin therapy resulted in a modest net benefit among patients with AF for whom warfarin was unsuitable.

Is an integrated stroke and bleeding risk score possible? Such an approach would assume that each risk factor carried equal weight, and (as highlighted above) this is not the case. Attempting to derive an integrated stroke and bleeding risk score may necessitate a score based on a complex multivariate model, with limited practicality and loss of simplicity for use in everyday clinical practice.

Also, given that the HAS-BLED score was designed to ‘flag up’ the patients at potentially high risk of bleeding, as well as to make clinicians think about the correctable bleeding risk factors—the clinical application of a bleeding risk score such as...
HAS-BLED would allow clinicians to make an informed assessment of their individual patient’s potential risk for bleeding per se (rather than guesswork) to be balanced against the stroke risk when management options are being considered.¹⁰⁸

Conclusion

Substantial advances have been made in the field of stroke prevention in AF, including greater awareness of stroke and bleeding risk factors, as well as therapeutic options including better anticoagulation control with VKA therapy and the NOACs. All these new developments have driven a paradigm shift in offering effective stroke prevention (which is, oral anticoagulation), for AF patients with ≥1 stroke risk factors.

Thus, the practice shift recommended in the 2012 focused update of the ESC guidelines is timely, given the primary initial focus on identification of ‘truly low-risk’ patients with AF, instead of having undue emphasis with the identification of ‘high-risk’ patients. Once the ‘truly low-risk’ AF patients have been identified (who do not need any antithrombotic therapy), appropriate thromboprophylaxis can be offered to all other AF patients.

Conflict of interest: G.Y.H.L. has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim, and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

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